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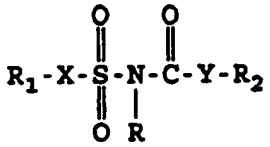
(54) Title: N-ACYL SULFAMIC ACID ESTERS (OR THIOESTERS), N-ACYL SULFONAMIDES, AND N-SULFONYL CARBAMIC ACID ESTERS (OR THIOESTERS) AS HYPERCHOLESTEROLEMIC AGENTS

(57) Abstract

The present invention is directed to compounds useful for the regulation of cholesterol of formula (I), methods for using them and pharmaceutical compositions thereof. In Formula (I) X and Y are oxgen, sulfur, or $(CR'R'')_n$ wherein n is 1 to 4; R is hydrogen, alkyl, or benzyl; R_1 and R_2 are phenyl, substituted phenyl, naphthyl, substituted naphthyl, an aralkyl group, an alkyl chain, adamantyl, or a cycloalkyl group.



(I)

2,6-diisopropylphenylacetyl chloride was replaced with adamantaneacetyl chloride;
^{1}H NMR($CDCl_3$): 1.21 (d, 12H), 1.6-2.0 (m, 15H), 2.15 (s, 2H), 3.4 (m, 2H), 7.15-7.25 (m, 3H) ppm.

EXAMPLE 5

Synthesis of Sulfamic acid[[2,4,6-tris(1-methylethyl)-phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester

(a) 2,4,6-Triisopropylbenzyl alcohol

A solution of commercially available 2,4,6-triisopropylbenzoyl chloride (35 g, 131.2 mmol) in 400 mL ether was added slowly to a suspension of lithium aluminum hydride (LAH) (4.89 g, 131.2 mmol) in ether (300 mL) at -15°C. The mixture was slowly warmed to room temperature over 18 hours. Saturated Na_2SO_4 solution was added slowly and the ether layer was separated, dried over $MgSO_4$, and evaporated to dryness. The compound was used in the next step without further purification;
NMR ($CDCl_3$): δ 1.2-1.4 (m, 18H), 2.8-3.0 (m, 1H), 3.3-3.5 (m, 2H), 4.8 (s, 2H), 7.1 (s, 2H) ppm.

(b) 2,4,6-Triisopropylbenzyl bromide

A solution of PBr_3 (2.7 g, 10 mmol) in ether (10 mL) was added slowly to a solution of 2,4,6-triisopropylbenzyl alcohol (4.68 g, 20 mmol) in 20 mL of ether at room temperature. The mixture was stirred for 1 hour, 5 mL of absolute EtOH was added, and stirring was continued for another 0.5 hour. The solvent was removed and the residue distributed between EtOAc and saturated Na_2CO_3. The EtOAc layer was separated, washed with brine, and dried over $MgSO_4$. The solvent was evaporated and the pure product was isolated by column chromatography (100% CH_2Cl_2, 3.5 g, 59%);
NMR ($CDCl_3$): δ 1.2-1.4 (m, 18H), 2.8-3.0 (m, 1H), 3.2-3.45 (m, 2H), 4.7 (s, 2H), 7.04 (s, 2H) ppm.

(c) Sulfamic acid[2,4,6-tris(1-methylethyl)phenyl]-acetyl]2,6-bis(1-methylethyl)phenyl ester

A solution of 2,4,6-triisopropylbenzyl bromide (12 g, 40.4 mmol) in dry THF (160 mL) was added to a suspension of Mg powder (1.96 g, 80.8 mmol) (4 hours) in THF (20 mL) heated under reflux. 2,6-Diisopropylphenoxysulfonyl isocyanate ($ROSO_2NCO$) (see Phos. and Sulf., 19:167 (1984) for preparation) (11.45 g, 40.4 mmol) was added neat, and after the addition was completed, the reflux was continued for another 2 hours. The reaction was stirred at room temperature for 16 hours. Saturated NH_4Cl and EtOAc were added. The EtOAc layer was separated, dried over $MgSO_4$, filtered, and evaporated to dryness. After purification by column chromatography (4:1 hexane:EtOAc), the compound was isolated as white solid (13.5 g, 67%), mp 178-180°C.

EXAMPLE 6

Synthesis of sulfamic acid[[2,4,6-tris(1-methylethyl)-phenyl]acetyl]-2,6-bis(1-methylethyl)phenyl ester sodium salt

This compound was prepared in the same manner as for the title compound of Example 2, except that the title compound of Example 1 was replaced with the title compound of Example 5, mp 250-252°C.

EXAMPLE 7

Synthesis of sulfamic acid(phenylacetyl)-2,6-bis-(1-methylethyl)phenyl ester

This compound was prepared in the same manner as the title compound of Example 5, except that 2,4,6-triisopropylbenzyl magnesium bromide was replaced with benzylmagnesium chloride (commercially available), mp 150-152°C.